抗精神病藥物療效濃度監測應用於換藥與個體差異之探討

Application of therapeutic drug monitoring in switching antipsychotics and analysis of interpatient variability

中文摘要

精神分裂症為一慢性、嚴重的心智方面疾病，近年來的研究顯示療效藥物之濃度監測可應用於精神疾病藥物治療最佳化之參考，以減少達成療效所需時間並降低可能產生之副作用發生率。台灣目前因將 thioridazine（TZ）列為觀察使用期，因此未來病患換藥期間若醫師採用延緩換藥模式，則可能產生藥物交互作用問題；此外，許多研究亦指出 olanzapine (OLA)之療效作用具個體差異，且可造成體重顯著上升，又經肝臟 CYP1A2 代謝後所形成之 N-desmethylolanzapine (DMO)被臆測具有平復代謝異常之作用。因此本研究第一部份收錄居住在療養院且服用 TZ 50mg/d 之精神病患（試驗組，n=3），經延緩停藥的模式換藥至 300mg quetiapine（QTP），於併用兩種藥物一週後，監測 QTP 藥物動力學參數，並以未曾服用 TZ 之病患為對照組（n=6）。研究結果顯示兩組經服用 QTP 兩週後的平均體重皆輕微上升但未達統計上顯著差異；而相較於對照組，試驗組之 QTP t1/2、Tmax、AUC0→∞、Vd 及 CL 分別增加 79.43%、10.00%、9.87%、79.99%及 53.99%，Cmax、trough level、AUC0→8 分別降低 40.09%、36.97%及 30.13%，但未達統計上顯著差異。本研究之第二部份研究目的則在利用高效液相層析儀搭配電化學檢測器（HPLC-ECD）來建立可同時分析 OLA 及其代謝物 DMO 之分析方法學，並以方便取得之 triprolidine 做為內部標準品；此 HPLC-ECD 系統對 OLA、DMO 標準品具顯著線性關係且 OLA 靈敏度達 1ng/ml、DMO 靈敏度達 0.5ng/ml；而分析藥物標準品經 C8 固相萃取管進行萃取後之精密度與準確度達規定標準；且可應用於病患之療效藥物分析；個別病患之 OLA/DMO 比值範圍在 6.609-144.892，顯示病患個體間之代謝差異。因此，本研究推論此換藥模式可能不適合原使用 TZ 之病患，因為低劑量使用 TZ 之病患經延緩停藥可能造成換藥目標藥物 QTP 之血中濃度下降，而是否造成病症控制上的影響，則需再評估。又本研究所建立之 OLA、DMO 分析方法可有效而方便應用於臨床療效藥物監測使用，病患個體間對藥物代謝之差異或 DMO 之藥效特質則需由更多試驗病患來證實。

英文摘要

Much evidence suggests that application of therapeutic drug monitoring (TDM) in antipsychotic treatment may shorten the dosing titration time and also optimize the therapeutic outcomes. Since thioridazine (TZ) is under evaluation in Taiwan and a drug interaction may occur when a switching strategy of delayed withdrawal was considered in switching antipsychotics. In addition, weight gain and interindividual variances have been associated with olanzapine (OLA). N-desmethylolanzapine (DMO), a metabolite of OLA by CYP1A2, was suggested to correlate inversely with certain parameters of metabolic syndromes. The first part of this study was to recruit schizophrenia patients (n=3) who have been treated with TZ 50mg/d in this switching trial and quetiapine (QTP) was titrated up to 300mg/d while TZ was delayed withdrawal (trial group). Pharmacokinetic parameters of QTP were determined at steady-state while six schizophrenia patients who also have similar QTP treatments but did not receive TZ before were used as control group. Slight weight gain was observed in two groups after two weeks of QTP treatment. Compared to the control group, the pharmacokinetic parameters such as $t_{1/2}$, T_{max}, $AUC_{0\rightarrow\infty}$, Vd and CL of QTP increased by 79.43%, 10.00%, 9.87%, 79.99% and 53.99%, and C_{max}, trough level and $AUC_{0\rightarrow 8}$ decreased by 40.09%, 36.97% and 30.13% in the trial group; however, there was no statistically significant difference. The second part of this study was to establish an analytical method for OLA and DMO using a high performance liquid chromatography coupled with an electrochemical detector (HPLC-ECD) while triprolidine was used as an internal standard. A linear calibration curve for each standard of OLA and DMO was established and the limitation of detection for OLA and DMO was 1.0 ng/ml and 0.5 ng/ml, respectively. Precision and accuracy of plasma samples spiked with OLA and DMO extracted by C8 solid phase met standard criteria. This HPLC-ECD system also has been applied in blood samples of schizophrenic patients (n=5) under OLA treatments and their OLA/DMO ratios ranged from 6.609 to 144.892 suggest a wide variance between interindividuals in metabolism. Our first part of study suggests that delayed withdrawal may not be an appropriate switching strategy in patient treated with TZ since there was drug interaction occurred; however, evaluation of patients' clinical response is needed before a dosing adjustment was concluded. Secondly, the HPLC-ECD analytical method established in this study was validated for OLA and DMO measurements and could be applied in routine TDM. More evidence is needed to elucidate the metabolic variance between interindividuals and the pharmacodynamics of DMO.